THE ADAPTIVE CHANGES OF HEART MUSCLE

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SYNOPSIS

Introduction. — The adaptive changes in the heart muscle are to be understood as the physiological and anatomical changes in its vital phenomena in response to changes in its

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environment. Such changes in environment are, by definition, stimuli (Verworn, '96). It is deduced from the work of Verworn ('13, 77) and Dolley ('22) that the primary effect of the stimulus upon the cell is always quantitative, though stimuli are both quantitative and qualitative. This is true for the effect of the stimulus in the functioning cell because of its specific differentiation which allows of only one functional product or capacity. That is, the muscle cell can only contract and the gland cell can only secrete its specific product. However, this one specific product or capacity may be the response to stimuli of different quality, namely, nervous, thermic, mechanical, chemical, or to a single quality of stimulus in different quantitative degrees, with the result that the intensity of the production of the specific product varies over a very wide range.

All such changes in the vital processes of the cell due to external conditions are the manifestations of its property of irritability. Irritability displays itself by two processes, excitation and depression. Excitation is characterized by increased response of the specific mechanism, depression by decreased response, depending upon the intensity, duration, and kind of stimulation. Consequently, the study of the adaptive changes in heart muscle is synonymous with the study of the reactions of the cell to stimulation and of the manifestations of the irritability of the cell.

The basis of comparative analysis. — The preliminary inspection of the fibers showed a great difference in the functional morphology between the fibers within the same animal and more strikingly a greater difference between the fibers in different individuals of the same species. Therefore, unless there is a fixed standard of comparison, a constant morphological criterion as in the nerve cell, characterizing the species, no exact comparison or analysis could be made.

The comparison of fiber with fiber, of group of fibers with group of fibers, and of animal of the species with animal of the species is based upon two criteria. The first of these is the constancy of the morphological picture of the heart muscle

fiber in metabolic nucleo-cytoplasmic equilibrium which contrasts it with all changes characteristic of excitation or depression. The second is the constancy of the numerical coefficient of the nucleus-plasma relation, which holds as a numerical law for the resting cell norm of the species (Dolley, '14). This numerical coefficient is the quotient obtained by dividing the figure representing the size of the cytoplasm alone by the size figure of the nucleus.

First, there will be defined what is meant by metabolic nucleo-cytoplasmic equilibrium. The term is used to designate the state in which there is no evidence of any embarrassment of the cell demonstrable morphologically or by a change from the normal nucleo-cytoplasmic coefficient. The numerical coefficient is the index of the reciprocal interchange of nuclear and cytoplasmic materials and consequently of cell metabolism. If the fiber is embarrassed by overexcitation, it is shown by the tables that the upset of this relation is in favor of the cytoplasm,—the coefficient becomes a larger figure than the norm; if the embarrassment is effected by depression, the upset is in favor of the nucleus,—the coefficient becomes a smaller figure. From the standpoint of the nucleus-plasma relation, the constancy of morphology and the constancy of the nucleus-plasma coefficient represent obviously the state in which the physico-chemical factors of anabolism and katabolism are in a state of equilibrium. To express this state of metabolic nucleo-cytoplasmic equilibrium of the muscle fiber, the term *metabiotic* fiber will be used. It is used because it expresses the balanced "way of life" of the normally functioning fiber.

The term metabiotic is also convenient because its root word permits the opposite variations of the metabolism of stimulation to be contrasted. A *katabiotic* fiber is one in which through either excitation or depression, the disintegrative processes predominate. An *anabiotic* fiber expresses one in a progressive process of upbuilding, such as the functional hypertrophy which results from regulated excitation.

The morphological identification of the metabiotic fiber.—In the metabiotic fiber, the nuclear membrane is regular and

shows no indentations, bulges, or wrinkles. The shape of the nucleus in longitudinal section is almost rectangular with its length about four times as long as the width (rat heart), although the ends are bluntly rounded. The ground substance of the nucleus stains with equal intensity and the chromatin network is regularly distributed over the whole area in thin filaments with small knots of chromatin at the nodal points. There is usually but one karyosome present. The cytoplasm has a distinctness which is unequalled in any other stage of the functional process. The sarcoplasm and the fibrillae stain uniformly throughout the fiber and show no evidence of edema or disintegration of the normal elements of the fiber. In conclusion, it can be said that the intensity of the staining of the nucleus and cytoplasm is uniform, which suggests a state free from embarrassment, while between them there is a relative intensity of staining whose constancy suggests an equilibrium in their state of interdependency.

In the case of either overexcitation or depression of the fibers, this relative intensity of stain does not hold.

The changes of excitation. — The earliest change in the individual fiber to overexcitation is a stage of hyperchromatism of the nucleus and an increase in the cross sectional area of the fiber and its nucleus. This increase in size is exactly proportionate between fiber and nucleus so that the metabolic relationship of the metabiotic fiber is retained in the first stage of excitation. Dolley has found an identical hypertrophy and hyperchromatism in the initial stage of excitation in both the nerve cell ('09, '13) and gland cell (unpublished work). Not only is there an identity of the nucleus-plasma coefficient but also the morphological picture is qualitatively identical, that is, both the structural elements and the proportionate relationship of the elements are identical. For this reason, there was no discrimination between these two stages, the less hyperchromatic stage and the more hyperchromatic stage of initial excitation, in the selection of metabiotic fibers for measurement. As Dolley has pointed out for the nerve cell, the relation of this stage to the metabiotic (resting cell) fiber duplicates the

relationship of the functionally hypertrophied fiber to the non-hypertrophied fiber. Function gives the same relationship as growth. The identity of the nucleus-plasma relationship and the qualitative morphological identity of the states indicates that the proportionate increase in size of both nucleus and cytoplasm in both immediate function and the resultant functional growth is the expression of a relatively greater rate of metabolism. The increased intensity of stimulation has increased the rate of this definitely proportionate reciprocal interchange.

The next change observed is a shrinkage of both the cross sectional area of the fiber and of the nucleus, but a greater shrinkage of the nucleus with a shift of the nucleus-plasma relation in favor of the cytoplasm. The nucleus remains hyperchromatic. This shrunken stage of the nucleus is also often associated with beginning edema of the sarcoplasm. This change in heart muscle is identical both in form and in its place in the process with the Hodge type of nerve cell.

The next change is the initial edema of the nucleus and the progressive edema of the cytoplasm. The subsequent adaptations to overexcitation are those of progressive edema of both the nucleus and cytoplasm with their consequent increase in size, with the exception of the final stage. The cytoplasm increases relatively more, so that there is a shift of the nucleus-plasma coefficient in favor of the cytoplasm. Coincident with the progressive edema, there is a progressive loss of chromatic material from the nucleus and from the cross striations. The edema and loss of chromatic material give objective expression to the shift of the nucleus-plasma coefficient in favor of the cytoplasm.

The final stage is a shrinkage of both the cross sectional area and of the nucleus. This is associated with a complete loss of chromatic material from the fiber and nucleus with the exception of the chromatic material within the karyosome. The striations are gone and are replaced by a foam structure, probably the effect of vacuolization. The nuclear shrinkage becomes again relatively greater. The process was thus followed

almost to complete organic exhaustion, with its final dechromatization of the nucleus. It corresponds in complete detail with the process of excitation in nerve and gland cells (Dolley).

Soon after the karyolysis of the nucleus becomes pronounced, certain changes begin at the ends of the nucleus. Up to this time, the longitudinal fibrillae (muscle columns) have seemed to be contiguous with the nuclear membrane, but at this time the cross striations at the ends of the nucleus begin to be disorganized. Instead of forming a continuous line across the fiber, the striations disintegrate and form a row of globules which retain the position formerly occupied by the cross striations. Later, the smaller individual globules fuse to form larger globules. This probably indicates the disorganization of the entire sarcomere with the fusion of the smaller globules into larger ones as the confines of the sarcomere degenerate. It seems to be one bit of evidence in favor of the view that the sarcomere has four walls which is still a theory to be demonstrated morphologically. The change in structure is accompanied by a change in the affinity for stains. As the striations change in form, they progressively lose their affinity for the basic stain and gain in intensity for acid stain.

This disintegration makes much more rapid progress in the direction of the length of the fiber than in its breadth. In fact, it may be so nearly confined to the center of the fiber that it seems that the section has undergone longitudinal splitting. It is this phenomenon, undoubtedly, that Wilks and Rindfleisch (cited by Goldenberg, '86, 88) thought was a true longitudinal splitting that would explain the mechanics of the production of heart hypertrophy. After the longitudinal splitting is well started, the disorganization spreads out in a radial direction from the nucleus as the center until the whole fiber has lost any evidence of cross striations and has few remaining fragments of the longitudinal fibrillae. It can be said for the rat and for the dog that the often mentioned "areas of undifferentiated protoplasm" at the ends of the nuclei are characteristic of an embarrassment of the fiber from excitation when they are of sufficient size to be recognized, and are never found in the metabiotic fiber or in the depressed fiber which is

uncomplicated by an initial excitation. Theoretically, there is a small cone of sarcoplasm at each end of the nucleus which does not contain fibrillae since the conception that the fibrillae course around the nucleus predicates the formation of such a cone. This cone becomes much enlarged and becomes demonstrable in the later stages of excitation, in which case the increased metabolic activity is associated with the using up of cell substance and consequent katabiotic changes around the nucleus.

The changes of depression. — The earliest change of depression is a shrinkage of the fiber and an absolute as well as relative increase in the size of the nucleus and in the nuclear materials. This stage of depression is best distinguished by its characteristic nuclear changes. The contour of the nucleus is well rounded but shows localized bulgings from its sides, usually in areas where the chromatin is most dense. The chromatin network is heavier and has larger and more numerous knots of chromatin at the junction of its meshes. The distension of the nuclear membrane inclosing an excess amount of stored chromatin demonstrates that chromatin is being made faster than it is being discharged. The considerable shift in the nucleus-plasma relation and the coincident increase in the absolute size of the nucleus demonstrate the shift of the reciprocal interchange of substance in favor of the nucleus. This evidence indicates that the cytoplasm is progressively unable to withdraw substances from the nucleus, but that nuclear syntheses continue for a time, from substances elaborated by the cytoplasm before the onset of depression. Eventually, the cytoplasm fails completely to give or take substances from the nucleus and becomes degenerated, as will appear.

In the cytoplasm, the materials are condensed so that Cohnheim's areas are rarely found in fibers cut in cross section. This contrasts the condensation of depression with the edema of excitation, as the latter conditions the formation of Cohnheim's areas in direct proportion to the degree of edema. The condensation is accompanied by a considerable increase in the intensity of the staining reactions of the cytoplasm. The

eosinophilic reaction as well as the chromatic reaction are increased, but the chromatic is predominant as shown by a faint violet tinge to the whole fiber as well as a much heavier staining of the cross striations. Whether the striations actually increase in volume cannot be stated, although their width and intensity of stain is apparently increased. This may be due to a simple condensation of the cross striations into a smaller cross sectional area.

This hyperchromatic depressed fiber can be distinguished from the hyperchromatic Hodge stage of excitation by the observation that the microscopical field containing Hodge fibers also contains a number of fibers in more advanced excitation. Also, the Hodge cell has a shrunken nucleus while this type of depressed nucleus is relatively and absolutely increased in size and has a tendency to bulge. This type of irregularity of the nuclear membrane, the shift of the nucleus-plasma relationship, and the marked intensity of the staining reactions differentiate the depressed from the metabiotic and the Hodge fiber.

The second nuclear change in depression is a shrinkage of the nucleus in its short diameter and a coincident increase in its length. This is consecutive to the same change in the fiber. This type of hyperchromatic nucleus is not so easily distinguished from the Hodge nucleus. Eosinophilia now becomes predominant in the cytoplasm and thus conforms to all depressions. The eosinophilia coupled with the changed form of the nucleus is sufficient, however, to differentiate this stage of depression from the Hodge fiber which is not eosinophilous and may even be edematous.

The characteristic changes of more advanced depression are the progressive shrinkage of both the cytoplasm and the nucleus and the progressive eosinophilia and regressive basophilic reactions which approach a hyaline condition of the fiber.

Changes of depression superimposed upon excitation. — While excitation and depression are found in pure states and are discussed as distinctly opposite phases of the same process,

they are often found superimposed one upon the other. It will be shown later that a single drug has the capability of acting as an initial excitant and a later depressant if the size of the dose or the duration of its administration is of a sufficient degree. It is evident, then, that it is possible to have a depressant effect superimposed upon an excitant effect by the continued administration of a single drug or by superimposing a depressant degree of any kind of stimulus upon an excitant degree of any stimulus.

Fibers have been put under conditions which were known to incite the changes of excitation and then the same fibers were put under conditions which were known to incite the changes of depression. The resulting morphological picture is a complex of the morphological changes associated with excitation and with depression. They show deeply stained nuclei packed with chromatin and supernumerary karyosomes, but the cytoplasm shows the depth of staining and condensation characteristic of depression, along with the globulation of cross striations and sarcomeres and the longitudinal splitting which are characteristics of the later stages of excitation.

Such a morphological complex is not found after superimposing excitation upon depression. It will be shown that the conditioning of excitation removes the restraint imposed by depression gradually, with less and less degrees of depression under the continued influence of the excitant conditions, until the morphological picture attains the state of the metabiotic fiber. It brings the fibers back to normal. Further conditioning of excitation simply carries the fiber through the same changes as any fiber not in depression.

In conclusion, a very important statement should be made, namely, that in all fibers, regardless of the degree of structural change induced by overexcitation or by depression, if there were any remaining cross striations, these striations were caught in all the different stages of contraction and relaxation.

Therefore, it is well established that there is a state of metabolic equilibrium, a metabiotic state, of heart muscle which can be differentiated morphologically from all other states of

heart muscle in either overexcitation or depression. Twenty-five of these fibers in cross section from each animal were drawn by the aid of the camera lucida, measured in area by the polar planimeter, and tabulated in Table I. The nucleus-plasma coefficient for the metabiotic fibers of the normal control dogs varies from 10.24 to 11.05, with an average of 10.65 for the eight animals, and the greatest variation is 7.6 per cent. The nucleus-plasma coefficient for the metabiotic fibers of the five normal rats varies from 10.90 to 11.62, with an average of 11.45, and the greatest variation is 7.1 per cent. This is a remarkable uniformity when it is taken into consideration that it holds for such a wide range of absolute size.

While these criteria hold with the constancy of a law, the absolute size of the metabiotic fiber varies over a great range. In the case of the normal control dogs, the average size of the metabiotic fibers is 216.89 square micra, but the range of size is from 174.49 to 304.01 square micra or a difference of 74 per cent. In the case of the normal rats, the average size is 166.95 square micra but averages from 113.35 to 257.30 square micra or a difference of 127 per cent. There is, consequently, a quantitative difference between one metabiotic heart fiber and another, between a group of such fibers and another group, and between the metabiotic fibers of one animal and another of the same species.

The functional hypertrophy, an anabiotic adaptation.

Data of experimental production. — Five dogs of the same litter were subjected to various degrees of activity. Three of the animals, of which only two will be used in this discussion, were subjected to various degrees of exercise in a treadmill and to free outdoor life. Two of the five were used as controls. Their relative degrees of activity will be indicated in later discussion. A more detailed account of this series can be found in a previously published paper on "The experimental production of hypertrophy in the nerve cell" (Collier, '22) which was based upon the nerve cells from these same animals.

Eight other young adult dogs were taken from ordinary life to establish a normal (Table I). The experimental animals should be checked against a normal average that would include animals both from active life and from a less active one. With this idea in mind, two of these animals, Normals 29 and 46, were adult country-bred dogs and two animals, Normals 28 and 30, were town-bred dogs. The supposition was that the farm-bred animals were more active than the town-bred animals,

TABLE I. NUCLEO-CYTOPLASMIC RELATIONS OF METABIOTIC FIBERS OF DOG AND RAT HEARTS

Animal	Cross sectional		Nucleus-plasma coefficient
	Area of fiber	Area of nucleus	
DOGS			
Normal Control Series			
Normal 28	208.75	18.57	10.24
Normal 29	304.01	25.91	10.79
Normal 30	195.42	16.41	11.05
Normal 32	185.80	15.86	10.71
Normal 33	187.84	15.66	10.99
Normal 34	187.05	16.41	10.39
Normal 35	174.49	15.00	10.63
Normal 46	291.80	25.48	10.46
Average	216.89	18.63	10.65
Experimental Control Series			
Muscular Exercise 45	141.54	15.51	9.12
Muscular Exercise 41	171.94	15.98	9.76
Experimental Hypertrophy Series			
Muscular Exercise 44	200.45	17.99	10.14
Muscular Exercise 42	252.22	21.84	10.50
RATS			
Rat 13	257.30	21.18	11.14
Rat 15	150.21	11.62	11.62
Rat 18	157.34	11.84	12.28
Rat 19	113.35	9.53	10.90
Rat 20	124.43	10.08	11.24
Average	160.52	12.85	11.44

especially since one of the latter was known to have been a pet house-dog. The other four dogs were chosen at random without any knowledge of their previous degree of exercise.

The morphology of the hypertrophied fiber does not differ in the least detail from that of the non-hypertrophied. And, although the range of size of these fibers varies widely, the index of the nucleus-plasma relationship remains constant in large as well as small fibers (Table I). The absolute size of the metabiotic fiber will be used as the index of the degree of anabiosis and the magnitude of the hypertrophy.

The correlation of this quantitative difference in size with the degree of excitatory stimulation manifested by function is suggested by a comparison of the town and country control dogs. The average size of the metabiotic fibers of the town-bred animals (Normals 28 and 30) is 202.08 square micra and of the corresponding fibers of the country-bred animals (Normals 29 and 46), 297.90 square micra. The difference between these averages is forty-seven per cent in favor of the relatively more active country dogs. The hearts of these two dogs, whose fibers were the largest of all measured, were diagnosed as hypertrophied from their gross size and the thickness of the ventricles as well as microscopically. This indication of a correlation of size with the degree of function is made conclusive by the proportionate increase in size of the fibers with experimental increase in the degree of function in the muscular exercise series.

The experimental control animals Muscular Exercise 41 and 45 which were confined throughout life for two and a half and three and a half years, respectively, had comparatively very small fibers. Muscular Exercise 41 which was killed at the beginning of the experiments had metabiotic fibers which average 171.94 square micra in cross sectional area, which is twenty per cent less than the average of the normal control animals. Muscular Exercise 45 which was killed at the end of the experiments had metabiotic fibers which average 141.54 square micra or thirty-five per cent smaller than the average of the normal control animals and seventeen per cent smaller than those of the experimental control killed at the beginning

of the experiments (Muscular Exercise 41). It is evident that the animals just discussed were in a state of relative katabiosis from underfunction, and in the case of Muscular Excerise 45 one may deduce a disuse atrophy after some degree of size has been attained, because the animal was confined for the last year in a cage with a floor space one-third as large as for the former two years and half. These animals are introduced here for the sake of comparison with the more exercised animals to emphasize the degree of hypertrophy and to indicate the great range in size correlated with different degrees of function.

Muscular Exercise 44 was allowed a year of outdoor life plus a small amount of work in the treadmill. The metabiotic fibers average 200.45 square micra or eight per cent smaller

TABLE II. LENGTH OF SARCOMERES IN MICRA

Normal 29	Muscular exercise 42	Normal 30	Muscular exercise 45
2.73	2.84	2.47	2.47
2.52	2.52	2.24	2.21
2.31	2.42	2.10	2.18
2.14	2.18	1.92	1.84

than the average of the normal control animals but twenty-one per cent larger than those of the experimental controls.

The most exercised animal, Muscular Exercise 42, was given regular exercise in the treadmill plus normal outdoor life for a year. Its metabiotic fibers average 252.22 square micra in cross section or twenty per cent larger than the average of those of the normal control animals and sixty-one per cent larger than the average of those of the two experimental controls. Actually, the exercise brought the size of this dog's fibers from one corresponding, presumptively, to the smallest size of the experimental controls to the third largest of all dog hearts measured, next to the known hypertrophy of the country dogs, Normals 29 and 46. These had had whole lives of exercise. Even Muscular Exercise 44 was brought to fifth place.

That there is an increase in the size of the fiber is confirmed by the fact that the increase in the cross sectional area of the fiber is accompanied by an increase in the length of the individual sarcomere. The data in Table II are the average measurements in micra of the sarcomeres in each of the four animals so studied. The four figures given under each animal represent four arbitrarily chosen degrees of contraction. The largest figure represents the length of the sarcomere in the relaxed condition. The smallest figure represents the length of the sarcomere in the most contracted condition. The two intermediate figures represent two intermediate stages. Each figure represents the average derived from the measurement of fifteen groups of sarcomeres, each group consisting of ten contiguous sarcomeres. Each figure represents, then, the average length of the sarcomere derived from the measurement of one hundred and fifty sarcomeres.

The animals with minimal exercise, Normal 30 and Muscular Exercise 45, had sarcomeres which were fourteen per cent shorter than those of the more exercised animals, Normal 29 and Muscular Exercise 42. These data demonstrate that the degree of anabiosis can be estimated either by the measurement of the cross sectional area of the metabiotic fiber or by the measurement of the length of the sarcomeres so long as contracted fibers are compared with contracted fibers and relaxed fibers with relaxed fibers. One set of data can also be checked against the other, which is of value since the fiber in cardiac dilatation is increased in length but the cross sectional area is decreased, as will be discussed more in detail later, whereas in hypertrophy both dimensions are increased. The figures of this table also demonstrate that it is possible to check the diagnosis of the state and stage of contraction or relaxation in a given animal by actual measurements of the length of the sarcomeres. It can be confessed that the reason for the measurement of the length of the sarcomeres was an attempt to check the diagnosis of the degree of contraction and the observation that such a mathematical diagnosis of the degree of contraction was possible was overshadowed by the accidental and much more important observation, for example,

in differentiating hypertrophy and dilatation, that the measurements of the length of the sarcomere have a definite relation to the data of the cross sectional area measurements.

The nature and significance of the functional hypertrophy. — Most discussions of hypertrophy are confused by the application of the same term to two or more different processes; to an increase in the size of the cell, to an increase in the size of the organ, and to an increase in the number of cells. The second confusion arising in the literature is the failure of the workers to differentiate between the two states of cell enlargement, that is, between hypertrophy proper and cloudy swelling. Virchow as early as 1858 defined hypertrophy as a true growth and differentiated it from the cell enlargement of degenerative changes by certain definite cytological differences ('58, 93).

The present conceptions of the nature and significance of hypertrophy appear to be divided between the pathological and the physiological.

The pathological conception of hypertrophy.

The identity of hypertrophy and degeneration. — Minot ('08, 71) says that hypertrophy is in itself a degenerative change and concludes the chapter with the following sentences. "Another form of degeneration which occurs in many cases is of great interest because it seems as if the cells were making a last great effort; and their performance is one of enlargement. This form of degeneration is termed hypertrophy." Minot is describing a state of katabiosis leading to exhaustion, namely, a cloudy swelling. It is not a true hypertrophy, that is, overgrowth.

A compensatory sequel to some pathological lesion. — The prevalent opinion seems to be, however, that hypertrophy is the result of degenerative changes. That is, since it occurs most commonly accompanying or following some pathological lesion, it appears to be the invariable result of a pathological "cause" and, therefore, to be of an abnormal character itself. Some of the commoner text book causes may be outlined as follows:

Compensation to inflammation.

General and coronary arterio-sclerosis of inflammatory (or non-inflammatory) origin.
Chronic fibrous myocarditis.
Acute exudative or chronic fibroid pneumonitis or emphysema.
Chronic interstitial nephritis.
Valvular deficiencies.

Excess fluid content of the blood (Munich beer heart).

Disturbed nervous control (Thyroid, suprarenal, vasomotor disorders).
Chemical irritation (Toxins and drugs).
Muscular work.

Physiological conception of hypertrophy. — The pathological conception of hypertrophy is so generally accepted that the one instance of hypertrophy which is not preceded or accompanied by a pathological lesion, namely, muscular overwork, is usually set aside as an entirely different proposition and designated as a physiological or even as an idiopathic hypertrophy. The latter term is used to express that there is no etiological pathological lesion and that hypertrophy happens, therefore, for some mysterious unexplainable reason. Nevertheless, some men have had the physiological conception of hypertrophy although initiated by a pathological lesion.

Rosenbach ('78, 9) attributes the mechanism of hypertrophy to a proportionate overwork of the contractile substance of the heart to compensate for the increased resistance to the blood flow.

Goldenberg ('86, 88) and a group of men working with him found by actual measurement of the fibers that heart hypertrophy is due to an increase in the size of the muscle fiber and not to an increase in the number of fibers. Goldenberg reviews the work of former investigators and states that J. Vogel, Kölliker, Foerester, Lebert, Hyrtl, and Rokitansky agreed that the state of hypertrophy is attained by a hyperplasia of the muscle fibers; that Wilks and Rindfleisch lay the increase in volume of the heart to an increase in the number of fibers to lengthwise splitting; that Hepp, Robin, Wedl, Bequel, Friedreich, Zenker, and Lancereaux measured fibers and found that the individual fiber is increased in size. Goldenberg concludes for the group who ascribe the hypertrophy to an increase in the size of the muscle fiber that function of the musculature gradually builds up not only a macroscopical increase in heart muscle volume, but also a microscopical increase in breadth of the heart muscle fiber through an inflow of material into the cell.

Hasenfeld and Romberg ('97, 371) have added the observation that the degree of hypertrophy is directly proportional to the magnitude of the valvular insufficiency which initiated the hypertrophy. This is in accord with the present work demonstrating that growth is quantitatively proportional to the intensity of the stimulus so long as the intensity is favorable for the production of hypertrophy.

Tangl ('06, 432) concludes that there is an increase in the diameter of the fiber which agrees with the findings of Goldenberg and with the data presented in this work. He also finds that there is an increase in the length of the hypertrophied fiber which I have confirmed by the measurements of the individual sarcomere with identical results. He agrees with the histological findings of Goldenberg and Leutelle that there is no evidence of mitosis of the cell nor any evidence of an amitotic division of the nucleus. He states that the histological evidence of inflammation was found in the later stages of hypertrophy, by which he means the edema and disintegrative changes of overexcitation, but he concludes that there is not sufficient proof of a consistent relationship between inflammation

and hypertrophy and with Leutelle ('88) is unable to define two types of hypertrophy, namely, a hypernutritive and a degenerative. It must be remembered that he is a contemporary of Minot and is denying the assertion that hypertrophy is a degeneration as Minot and others thought and is concluding in favor of a physiological significance for the process of hypertrophy.

At the same time, Kulbs ('06, 28) became dissatisfied with the explanation that cardiac hypertrophy is the reaction to a pathological necessity. He used treadmill exercise to produce a hypertrophy that would be uncomplicated by valvular insufficiencies, arterio-sclerosis, kidney diseases, etc. He removed all pathological conditions from his experimental method and produced his hypertrophies by simply working his dogs in a treadmill in a manner similar to the method which I used. His results were identical with those obtained in the course of the present work which are tabulated in Table I.

The mechanism of the organic relationships involved in hypertrophy of the heart. — Such data demonstrate a correlation of quantitative differences in size with quantitative degrees of body function. This relation has been concisely stated by Hirsch ('00), "The mass of heart muscle is the expression of the degree of body work." The most important theories to explain this correlation are the mechanical and the nervous. The nervous side is fully accepted but not to be discussed in detail because it belongs to the general nervous control of the heart. A mechanical theory will be discussed to show that the principle underlying the production of hypertrophy is identical in all cases, whether due to increased resistance conditioned by body work or by a pathological lesion.

Muscular exercise distends the heart through forces working from both the venous and the arterial side. Tension is applied from the venous side in two ways: the increased respiratory movements accompanying muscular exercise suck a greater amount of blood into the right auricle in a given period of time and the increased muscular contractions milk the blood out of the capillaries and veins into the heart; thus increasing the venous pressure and the tension upon the right side of the heart during diastole (Howell, '11, 508–9). From later statements from the same author, the conclusion can be drawn that the amplitude of the venous pressure determines the intensity of the stimulus to contraction which determines the rate and the amplitude of the contraction (Howell, '19, 552).

The work of Tangl and Zunst ('98, 544) demonstrates that muscular activity increases the arterial blood pressure from 117 mm. to 238 mm. of mercury in the case of the dog doing work quite comparable to the treadmill work. Thus from the arterial side as on the venous side, tension is placed upon the heart during diastole. H. A. Stewart ('11) says, "Hypertension applied to the ventricular wall during diastole is a most potent factor in increasing the force of systolic contraction." This may be accepted so long as the degree of tension and the nutritional state are within certain limits.

Likewise, the pathological lesions act to produce either a general increased tension, as just discussed, or a local one.

A local increased tension conditioned by a pulmonary stenosis, by an increased resistance to the blood flow through the lungs, by arterio-sclerosis, by chronic nephritis, by excess fluid, or by an aortic stenosis would only distend a local portion of the heart and stimulate it to overwork unless the stimulus was of such a degree that it in turn affected other portions.

Thus, regardless of whether the hypertrophy produced is "caused" by a valvular deficiency, a pneumonitis, a myocarditis, an interstitial nephritis, an excess fluid content of the blood, an arterio-sclerosis, or, as is demonstrated in this paper, body overwork, the common effect is that of a relatively greater tension upon the muscular walls of the heart as a whole or locally, conditioned upon a relative or absolute increase of resistance. Thus, Stewart's hypertension theory accounts for a great variety of localized cardiac hypertrophies and Howell's venous hypertension theory furnishes a basis for the regulated hypertrophy of the whole organ in certain conditions. The objection to Stewart's theory as an all sufficient theory to explain hypertrophies is that he deals with mechanical to the exclusion of nervous and chemical stimulation.

The rest of the text book causes, exophthalmic goiter, vasomotor and suprarenal disorders, chemical irritants, either toxins or drugs, and the reflex-nervous excitation of the heart in overwork can affect the heart only quantitatively through the normal nervous control or through the conductile mechanism of the heart or through both by increasing the rate and

intensity and conductivity of stimulation. Consequently, regardless of the kind of stimuli, mechanical, nervous, or chemical, all the "causes" have a common effector, overstimulation, and the conclusions drawn for one stimulus are applicable to all. The experimental data of the next section will entirely exclude any specificity of stimuli.

The term "cause" has been used in this discussion because it is the absolutely necessary term to convey the interpretation that the text book writers place upon the etiological significance of the relationship of these pathological lesions to the cardiac hypertrophy. Speaking for the heart, there is no foundation for any cause and effect relationship because any of the above named pathological or physiological factors may condition either hypertrophy or organic exhaustion and atrophy or depression and atrophy, which will be discussed at length in the following section, depending upon the rate and intensity of the stimuli and the nutritional state of the fiber. Thus, hypertrophy is not *caused* but may be *conditioned* if the rate and intensity of the stimuli and the state of nutrition are favorable. For the same reason the term "compensatory" hypertrophy is objectionable. There is no inherent purpose to compensate invested in the properties of the cell because if the stimuli are of insufficient rate and intensity, the hypertrophy does not compensate; if the stimuli are of too great rate and intensity, the hypertrophy does not compensate and, in fact, may go to organic exhaustion and atrophy; but if the rate and intensity lies between these two extremes and if the nutritional state is sufficient, hypertrophy is conditioned and affords physiological adaptation for the preëxisting deficiency. The only conception that accounts for the initiation of hypertrophy as well as for the failure of its initiation is that of conditionality. It is upon this idea that the physiological interpretation of the etiology of hypertrophy is based. The physiological conception of the incidence of hypertrophy following a pathological process is that it is the adaptation to the altered relation of the normal properties of the cell influenced by the pathological process.

The cellular mechanics of hypertrophy. — Hypertrophy, or growth after cell maturity, is the physiological-anatomical manifestation of an increased metabolism initiated by a quantitatively greater degree of stimulation.

Its cellular mechanics are based upon the fundamental property of irritability coördinated with the equally fundamental property of metabolism. Thus, Thoma says that, as R. Virchow showed, growth, irritability, and metabolism are the three interdependent vital phenomena of the cell. If these three fundamental properties are interdependent, it can be deduced that there is no specificity of stimuli. This will be experimentally demonstrated for the heart in the next section. Verworn defines the irritability of living substance as, "Its ability of reaction to changes in its environment by changes in the equilibrium of its matter and energy"; and, "changes in its environment," he calls stimuli ('96, 353). Consequently, if the presence of hypertrophy depends upon stimulation, the conclusions derived for any one stimulus are applicable to all kinds of stimuli.

The data presented in Tables I and II and the text of the foregoing discussion demonstrate that the size of the fiber is directly proportional to the degree of cardiac stimulation. The next step is to correlate stimulation with metabolism.

These quantitative changes in the size of the cell and, it will be shown, their corresponding quantitative intensities of specific energy production are the manifestations of "the changes in the equilibrium of its matter and energy." These changes are functions of cell metabolism involving upon the assimilative side the formation of the more complex substances from the simpler substances gained from the blood with the storing of potential energy; and, upon the dissimilative side the reduction of the more complex compounds of the cell into simpler compounds with the coincident liberation of the stored potential energy in the form of kinetic energy manifested for the most part in the performance of function. It follows that growth is the manifestation of the assimilative side of metabolism and that functional energy production is the manifestation of the dissimilative side of metabolism. In the metabiotic

fiber, the dissimilative processes are exactly balanced by the assimilative processes, as demonstrated by the constancy of the nucleus-plasma coefficient. Since the intensity of the liberation of energy for function, which is the manifestation of the dissimilative side of metabolism, is increased in the hypertrophied fiber, the assimilative side of metabolism, growth (hypertrophy), must be correspondingly increased. The metabolic nucleo-cytoplasmic equilibrium of the non-hypertrophied cell is retained in the hypertrophied cell which demands that if one phase of metabolism is increased that both phases, assimilatory and dissimilatory, must be increased. This seems to allow only of the conclusion that an increased size of the cell and an increased production of functional energy are accomplished by an increase in the rate of the non-hypertrophied cell metabolism. Consequently, the intensity of the specific energy production, work, and the size of the cell are the manifestations of a quantitatively greater rate of metabolism.

Verworn states this relationship of size and function not upon the basis of metabolism as it has been developed here, but upon the obvious anatomical relationship. "Die Intensität der spezifischen Energieproduktion einer Ganglienzelle eine Funktion der Masse ihrer entladungsfähigen Substanz ist," and states that this law laid down for the nerve cell also applies to the muscle cell, "Eine grösserer Masse eines explosiben Stoffes liefert bei der Explosion natürlich eine grössere Menge Energie als eine kleinere Masse; ein grösserer Muskel produziert bei gleichstarker Reizung mehr Energie als ein kleinerer" ('07, 131). Thus the size of the metabiotic fiber determines its intensity of specific energy production.

Therefore, in conclusion, both the intensity of the specific energy production and the size of the fiber are the manifestations of a quantitative rate of metabolism. The relationship of stimulation to irritability, namely, "changes in the equilibrium of cell matter and energy," of which cell metabolism, cell function, and cell size are manifestations, is quantitative. A greater degree of stimulation induces a greater degree of irritability which is manifested by a greater rate of metabolism;

this, in turn, conditions a greater intensity of function and a larger cell so long as the rate and intensity of the stimuli are adjusted to the nutritional state of the fiber.

The view of adaptation as the resultant of the increased degree of stimulation is applicable to all forms of hypertrophy, and, conversely, all hypertrophies are referable to the fundamental principle, already stated, that the physiological-anatomical complex of function, metabolism, and growth is the objective manifestation of any excitatory stimulation. The same view is equally applicable to the failure of hypertrophy under its usual conditions, — the stimuli may be deficient or excessive in duration and rate, so that disuse atrophy or exhaustion atrophy are equally provided for. So far as concerns the hypertrophy proper, namely, the increase in size of the cell unit, the distinction between simple and pathological hypertrophies is nonexistent. All hypertrophies are physiological in origin and nature, although they may reach a pathological state in their degree, and, in fact, they usually do.

Katabiotic adaptive processes. — The discussion has been heretofore confined to a regulated overexercise in which the factors of anabolism and katabolism are in a state of equilibrium. Katabiosis is the process that results if the rate and intensity of stimulation and the nutritional state are not favorable for one or all fibers at a particular time. Thus, this section of the paper is concerned with an upset of the condition of metabolic nucleo-cytoplasmic equilibrium by overexcitation or depression. The study of the cytomorphosis correlated with degrees of stimulation has been experimentally undertaken by the use of trophic, thermic, nervous, and various chemical stimuli in various degrees and dosages and over various periods of time.

However, such changes of stimulation are present in a less degree in all normal animals. Moreover, in all of the dogs discussed in the foregoing section, there were katabiotic fibers as well as metabiotic fibers, that is, the rate and intensity of stimulation were not altogether suitably adjusted to the metabolism. They were tacitly ignored at that time to avoid confusion.

It was because of the presence of these katabiotic fibers that the diagnosis of the metabiotic state was indispensable for comparison. Metabiosis is a state. Katabiosis is a process which has many degrees, the magnitude of which may be

TABLE III. DATA OF DRUG ADMINISTRATION

Animal	Weight in grams	Dose per day	Duration ot experiment	Total dosage
		Digitalis Series		
10	130	.006	10 days	.06
11	180	.006	42 days	.252
23	160	.024	17 days	.408
27	150	.006	30 days	.543
		.024	21 days	
		.0015	14 days	
28	200	.0015	30 days	.045
30	220	.0015	21 days	.0315
		Cocaine Series		
4	....	.20*	3 days	1.20
5	....	.20*	2 days	.80
3	....	.20*	1½ days	.60
		Pilocarpine Series		
2	120	.3†	89 days	26.7
1	125	.3†	100 days	30.0

* Twice daily. † Rest every third day.

roughly determined by the change of the index of the nucleo-cytoplasmic relationship above or below that of the metabiotic fiber.

Experimental data. — Most of the data presented in conjunction with this portion of the paper are derived from rat hearts, the remainder from dogs. The fact was appreciated that the use of two species of animals would furnish a more general basis for deductions. Of the thirty rats used, five were normals. The dosage and the duration of the drug administration are given in Table III.

Rats 16, 17, 24, 25, and 30 compose a series of experiments to demonstrate the correlation of morphological changes with the partial or complete deprivation of the rat of its oxygen supply. The method used to eliminate the greater part of the oxygen was to substitute hydrogen for air by passing a stream of hydrogen through an enclosed chamber.

Rat 16 was subjected to three consecutive hours in the hydrogen chamber.

Rat 17 was subjected to two shifts of ten hours each during which time pure air was admitted for ten minutes in every forty. There was a period of fourteen hours rest outside of the chamber between the two shifts. The animal was killed by asphyxiation in the chamber.

Rats 24 and 25 were subjected to the same experiment in the same way as Rat 17 except that the period was four times as long.

Rat 30 was subjected to the same method in the same way for a period of seventy days with a period of rest of seven days from the eighth to the fifteenth day.

Rat 26 was subjected to a temperature of 40° C. in a well-ventilated oven for two and one-half hours per day for three weeks. The object was to ascertain the effect of heat on so highly specialized an organ as the heart, bearing in mind the general law that heat within certain limits of degree increases the rate and intensity of the fundamental processes of the cell.

Rat 6 was operated upon and one kidney removed. It was killed two days after the operation from which the animal had not fully recovered.

Rat 9 was given a very small dose of caffein per day for ten days in order to produce the intercalated discs which are associated, in the literature, with caffein administration.

Four dogs were used to demonstrate that the changes described in detail for the rat are also common to the dog in every respect. However, the dog's heart is more resistant to these changes than the heart of the rat. It is possible that this fact is due to the greater rate of contraction in the rat which would permit less time for recuperation. Its adaptive powers would thus be more limited.

Muscular Exercise 43, which was described in the data for the functional hypertrophy, was in a toxic state from infection.

Dog 36 was given strychnine continuously until the lethal dose produced death six hours after the beginning of the experiment.

Dog 37 was a rabid animal which had passed through the excitation stage and was in a state of coma when it died.

Normal 31 demonstrated a cardiac functional disorder on the cardiagram which was diagnosed by the physiologist as an abnormal vagus stimulation.

Mechanics of katabiosis from overexcitation. — The morphological evidences of katabiosis from overexcitation which have been explained in detail in the previous section are: the progressive edema, the loss of chromatin from the nucleus, the

disintegration of the cross striations to the degree of metamorphic change, the breaking up of the sarcomeres, and the vacuolization of the sarcoplasm. The progressive edema is the manifestation of an increased osmotic pressure which Cook ('98), Loeb ('94), and Stewart ('11) have demonstrated in the immediate reaction to overstimulation. The majority of the writers favor the opinion that muscular contraction and relaxation are based fundamentally upon the physico-chemical reactions of the cross striations. An increased rate and intensity of excitatory stimulation is quantitatively associated with a conversion of the cell structure into energy as is made evident by the loss of chromatic material from the cross striations and from the nucleus and the disintegration of the cell structure. The alterations demonstrate that the destructive process of the fiber exceeds the constructive process. Thus, in overexcitation, the duration and rate of the stimuli are of such a degree that the metabolism of that moment is unbalanced in favor of the oxidative destructive changes, and, if the duration and rate of the stimuli are not altered in degree to allow for recuperation, the destructive phase of metabolism becomes progressively predominant and the metabolism recedes progressively farther from the state of metabiosis.

The metamorphic change of the extranuclear chromatin in the cross striations, which has been discussed as a characteristic change in the latter stages of overexcitation, is clearly the end phase of an identical regressive process. The regressive process is made evident by a gradual decrease in the affinity of the cross striations for hematoxylin. From the point of view of staining reactions, it seems that the extranuclear chromatic material as well as the nuclear material is used up in overfunction, for the regressive intensity of staining approaching the metamorphic change of the cross striations occurs concurrently with the progressive diminution of nuclear substance.

Mechanics of katabiosis from depression. — Measurements have shown that in depression the cross sectional area is decreased but the length of the sarcomere is increased. This is still in accordance with the statement that the volume of the

sarcomere is decreased, because the increase in length is disproportionate to the decrease in area. However, the shrinkage in volume does not seem to account for all of the increase in substance per unit volume. At least, the simple explanation of shrinkage will not account for the denser staining of the nucleus, because in the early stages of depression the volume and amount of chromatic substance is both relatively and absolutely increased.

From the analogy with other depressions, part of the increased eosinophilia of the cytoplasm may be due to an increased density of substance following an assimilation of raw foodstuffs which are not synthesized into cell structure. Popoff ('09) demonstrated the inability to synthesize raw food into cell structure in the case of depressed paramaecia. A year earlier ('08), he found that yolk material, fat, and glycogen are deposited in the cytoplasm of depressed metazoan sex cells, and, still earlier, that eosinophilius granules are deposited in depressed somatic cells ('07). Reichenow ('08) found unsynthesized food in the intestinal epithelium of the depressed frog. Dolley ('13) found an opacity associated with eosinophilia as well as discrete eosinophilic globules in the depressed nerve cell, both of which he interpreted as unsynthesized albuminous material. Further, as the infiltration of fat and glycogen occurs in the depressed nerve cell, they would be expected also to occur in depressed cardiac fibers and fatty deposits were actually found.

The piling up of substance within the fiber is a demonstration that the metabolism of depression is relatively different from that of excitation, which is characterized by a diminution of substance. This diminution of substance in the latter case is accomplished by a predominance of oxidative or dissimilative processes over assimilative processes. It can be deduced that the increase of substances in the case of depression is accomplished by a retarding of the oxidative processes. First, because depression was experimentally produced by creating as complete an anoxidative metabolism as possible, the hydrogen gas substitution series. Second, because the diminution or absence of function which occurs in depression is the

manifestation and therefore the index of the degree of the dissimilative phase of metabolism. This deduction is in accord with Verworn ('13, 238).

The progressive condensation, approaching the final stage of hyaline metamorphosis, demonstrates a metabolism leading to a degenerative state. Morphologically, this is demonstrated by a progressive condensation of structures throughout the process, indicating that the hyaline condition is gradually approached. It seems most probable, then, that the factors which condition the gradual condensation also condition the hyaline degenerated state if carried to a sufficient degree over a sufficient period of time.

From the nuclear side, there is evidence that the stuffing of the nucleus with newly formed nuclear material is not without katabolic significance.

Efficient metabolism depends upon the reciprocal interchange of nuclear and cytoplasmic substances. In depression, the nuclear material is retained within the nucleus so that the reciprocal interchange is obviously impaired. The appearance of the chromatin in the depressed nucleus is not typical and may be due to the incomplete formation of the substance. The material is diffuse and is not formed in discrete granules as in the normal fiber. The condition might also be interpreted as a karyolysis after having been once completely formed. The ascribing of a karyolytic significance is further given some foundation by the observation of the later nuclear changes in which the nucleus shrinks and becomes elongated. Finally, not only is the nuclear content diminished but also the chromatic material of the cross striations disappears completely when depression reaches the state of hyaline change.

Mechanics of anabiosis in excitation following depression. — The katabiotic process of depression is conditioned by a relative asphyxiation of the fiber because of an incapability of using oxygen in its metabolism. Materials are stored in the cell but they are incompletely synthesized because of the impaired metabolism. After the restraint of depression is removed, those substances which the fiber was incapable of using can

now be utilized in cell metabolism. The result is a rapid increase in size of the fiber and an increased functional capability of the organ which is a true anabiosis.

Mechanics of katabiosis in depression following excitation.— The observation that the alterations produced by excitation persist and upon them are placed the changes peculiar to depression demonstrates the fact that depression will not nullify the changes produced by excitation. Depression following excitation does not bring the fiber back to normal metabiosis as does the opposite, excitation following depression. The reason is that depression introduces conditions which are abnormal, deficient oxidation, anoxidative disintegration and storage of unsynthesized food.

Analysis of the action of stimuli. — Each animal represented in Table IV has two sets of figures. The first and invariably the smaller set of figures represents the average of twenty-five of the most nearly metabiotic fibers or if depression were present, of the most depressed fibers. The second set represents the average of the most edematous fibers. The two exceptions to this rule are Rat 28 of the digitalis series and Dog 36 after strychnine in which all of the fibers were edematous. The functional state as stated in the second column is based upon the cytological diagnosis of the fibers measured. In each instance this diagnosis based upon morphology is checked by the nucleus-plasma coefficient. The different coefficients obtained can be arbitrarily divided into three groups. The middle group has practically an identical coefficient, that of the metabiotic fiber which has been definitely established for the heart muscle fiber in the first section (Table I). Table IV shows that all coefficients with a numerical value below that of the metabiotic fiber are obtained from the measurement of depressed cells, and all coefficients with a numerical value above that of the metabiotic fiber are obtained from the measurement of excited cells. Not only is the numerical value of the nucleus-plasma coefficient diagnostic of the states of metabiosis, depression, or excitation, but it is also a valuable index of the degree of excitation or depression.

TABLE IV. COMPARATIVE DATA OF MEASUREMENTS OF KATABIOTIC HEART FIBERS

Animal	Functional State	Cross sectional area of		Nucleus-plasma coefficient		
		Fiber	Nucleus	Depression	Metabiosis	Excitation
		RATS				
		Digitalis Series				
29	Excitation	187.56	12.09	....	....	14.51
	Excitation	341.36	17.99	....	....	17.97
28	Excitation	420.49	17.39	....	....	23.17
10	Metabiosis	218.11	17.01	....	11.82	....
	Excitation	425.32	22.17	....	....	18.18
11	Depression	115.67	11.64	8.94	....	....
	Excitation	222.31	13.95	....	....	14.94
23	Depression	75.90	11.67	5.54	....	....
	Depression	109.98	13.59	7.09	....	....
27	Depression	131.63	12.74	9.33	....	....
	Metabiosis	215.84	16.84	....	11.81	....
	Excitation	290.86	17.61	....	....	15.52
		Pilocarpine Series				
1	Depression	90.41	10.51	7.60	....	....
	Depression	229.00	19.32	10.58	....	....
2	Metabiosis	245.04	19.21	....	11.75	....
	Excitation	454.31	24.25	....	....	17.73
		Cocaine Series				
3	Excitation	230.77	15.22	....	....	14.16
	Excitation	433.77	20.00	....	....	20.68
5	Depression	119.86	11.41	9.50	....	....
	Excitation	214.07	10.86	....	....	18.71
4	Depression	125.37	12.23	9.25	....	....
	Excitation	187.03	10.63	....	....	16.59

TABLE IV. — Continued

Animal	Functional State	Cross sectional area of		Nucleus-plasma coefficient		
		Fiber	Nucleus	Depression	Metabiosis	Excitation
		Hydrogen Gas Substitution Series				
16	Depression	102.84	14.52	6.08	....	....
	Excitation	199.44	14.73	....	....	12.54
17	Depression	144.84	17.87	7.10	....	....
	Excitation	179.28	13.29	....	....	12.49
24	Depression	123.54	15.18	7.14	....	....
	Excitation	188.47	14.62	....	....	11.88
25	Depression	105.81	10.52	8.96	....	....
	Excitation	151.79	10.81	....	....	13.03
30	Metabiosis	201.55	16.09	....	11.52	....
	Excitation	424.78	22.93	....	....	17.52
		Heat				
26	Excitation	141.27	9.75	....	....	13.16
	Excitation	233.57	15.51	....	....	14.06
		Shock				
6	Excitation	182.55	13.19	....	....	12.84
	Excitation	320.00	15.10	....	....	19.19
		Caffein				
9	Excitation	250.75	17.50	....	....	13.33
	Excitation	333.32	16.24	....	....	19.52
		DOGS				
		Bacillary Septicaemia				
M. E. 43	Depression	183.73	21.27	7.64	....	....
	Excitation	361.28	19.42	....	....	17.60

TABLE IV. — Continued

Animal	Functional State	Cross sectional area of		Nucleus-plasma coefficient		
		Fiber	Nucleus	Depression	Metabiosis	Excitation
		Abnormal Vagus Stimulation				
N. 31	Depression	221.36	20.64	9.73	....	....
	Excitation	273.13	17.75	....	....	14.39
		Rabies				
N. 37	Depression	128.28	15.68	7.18	....	....
	Excitation	231.13	14.62	....	....	14.80
		Strychnine				
N. 36	Excitation	216.40	15.67	....	....	12.80

No portion of the experimental work is more instructive and furnishes more conclusive evidence of the functional significance of these cytological changes than the digitalis series. The whole range of functional cytomorphosis was induced by varying the dosage and the period of administration of this one drug. It will be made the basis of discussion and the other agencies will be discussed in comparison with it.

Rat 29 was given the smallest dosage in the digitalis series over a period of three weeks. It showed edema, longitudinal splitting of the fibers, and disintegration of the cross striations and sarcomeres, all of which have been described as adaptive changes characteristic of overexcitation. Because of the marked edema and a metabolism favoring the cytoplasm, these changes are expressed mathematically by a shift in the nucleus-plasma coefficient in favor of the cytoplasm. The edema was so great that some of the fibers showed vacuolization. There were a number of hyperchromatic fibers present (first set, Rat 29) but no metabiotic fibers were found. They gave a nucleus-plasma coefficient which was twenty-six per

cent greater than that of the metabiotic fiber, and were principally of the Hodge type. The fibers in the later stages of excitation (second set) have a nucleus-plasma coefficient which is twenty-three per cent greater than that of the most edematous fibers of the average normal animal.

Rat 28 was given the same sized dosage over a period of four weeks. Practically the same changes were found in this animal as in the animal not administered the drug for as long a time (Rat 29), but the degree of excitation was greater than in the latter case. The most edematous fibers had a nucleus-plasma coefficient which was sixty per cent greater than that of the most edematous fibers of the average normal rat. Another index of the degree of excitation was expressed by the preponderance of hypochromatic overexcitated fibers, almost to the exclusion of hyperchromatic less excitated fibers.

An identical sequence of changes was found in Rat 26 which was subjected to moderate heat, in Rat 6 which was suffering from operative shock, and in Rat 9 which was given caffein. While the quality of the change is identical in all cases, there is a quantitative difference between them which can be roughly estimated by their respective nucleus-plasma coefficients found in Table IV.

In the next group in the digitalis series (Rats 10 and 11), a larger dose was administered (Table III). Rat 10 was given this dosage for ten days. The effect on the cytology of the cell was that of a moderate excitation upon which was superimposed a very slight depression. There were still many metabiotic fibers present. Rat 11 was given the drug for three times as long as Rat 10, and showed a very much more marked depression superimposed upon the primary excitation than was found in Rat 10. The fibers were shrunken in cross sectional area and the sarcomeres were increased in length. The nuclei showed an accumulation of chromatin and accessory karyosomes, both of which are characterisitics of depression. The cytoplasm showed the globulation of the sarcomeres and longitudinal splitting of the fibers, which are characteristic of excitation, but instead of the vacuolization and edema which is usually associated with this globulation and longitudinal

splitting, the sarcoplasm was condensed into an almost hyaline staining substance which is characteristic of depression. Hence, the changes of depression were found superimposed upon those of excitation. The most hyperchromatic fibers had a nucleus-plasma coefficient which was twenty-eight per cent less than that of the normal metabiotic fiber and very few edematous fibers could be found.

Rat 23 of the digitalis series was given a still greater dosage, sixteen times as large as the first group of the series and four times as great as the second group. The cytological changes were those of depression but even in a greater degree than found in Rat 11. The period of excitation had evidently been shorter and the depression more intense. The fibers had shrunken to less than half the cross sectional area of the average normal fiber and the nucleus-plasma coefficient of the hyperchromatic fibers was fifty-one per cent below that of the average normal metabiotic fiber. Its most edematous fibers had a nucleus-plasma coefficient of a smaller value than that of the metabiotic fibers of the average normal animal.

It is demonstrated by comparison of Rats 10 and 11 that the same dosage over a longer period of time produces the greater depression, a depression equal to that induced by a larger dose of the drug (Rat 23). This secondary depression from the continued administration of the same sized dose of the same drug is evidently a cumulative effect which is equal to the administration of a larger sized dose. The cocaine series further demonstrates this cumulative effect.

Rat 3 was given a dose of cocaine every twelve hours for a day and a half with the result that the heart showed marked excitation. Rat 5 was given the same sized dose with the same interval between doses but for a longer period of time, two days. It showed the characteristic changes of depression superimposed upon those of excitation. Rat 4 was administered the drug in an identical manner but for a still longer period of time, three days, with the result that a very marked depression was superimposed upon the changes of excitation. Consequently, a drug which in single doses induces an excitation may induce a secondary depression if the drug is continued over a sufficient

period of time or if the doses are given without a sufficient interval of time between doses because of the cumulative effect.

The depressions induced by the drugs that have been considered so far were secondarily superimposed upon primary excitations. In an attempt to secure a primary depression uncomplicated by an excitation, oxygen was removed from the animal chamber to a large degree by replacing the air in the chamber with hydrogen mixed with air. While a primary depression was not fully accomplished because certain stimuli acted centrally upon the nervous system resulting in reflex excitatory stimuli to the heart, as the initial excited state suggests, the duration and degree of the excitation were practically negligible.

Rat 16 was subjected to such oxygen deprivation for three hours, until the death of the animal. It showed a marked depression in many of its fibers. Rat 17 did not receive such severe treatment but was kept under the experimental conditions for a longer period of time. While the nucleus-plasma coefficient of its fibers does not show a much greater depression than that of Rat 16, a much greater number of fibers were affected in the former animal. Rats 24 and 25 were treated similarly to Rat 17 but for a period four times as long. Both rats showed some depression but Rat 25 showed a much less degree than any of the animals of this series which have been considered so far. Rat 30 which was kept under the experimental conditions for a period eight times as long as Rats 24 and 25 showed very little evidence of depression. Many of its fibers were metabiotic and most of them were normal as shown by its nucleus-plasma coefficient in Table IV. The conclusion can be drawn from this data that the organism becomes adapted to a changed environment and its metabolism is established upon a new basis. While the heart fibers became normal, the animal lost weight and became progressively more lethargic.

The last animal of the digitalis series, Rat 27, was given the dose of the drug which was known to produce a depressant affect and then was given the same drug in a dose that was known to have an excitant affect. It was possible to find

fibers with the changes characteristic of excitation and others with those characteristic of depression. However, they did not complicate one another in the same fiber as in the case of Rats 11 and 23. The two phases were confined to separate fibers to a surprising degree. A cross-sectional area of the ventricle showed groups of edematous fibers interspersed with groups of more deeply staining fibers. The final excitation phase predominates in the animal and leaves no trace of a former depression in such fibers as are affected by the excitation because the return from depression is the normal process of recovery hastened by the stimulation process. The resistance of depression, that is, the inhibition of oxidative processes, was removed and the conditions of excitation hasten the recovery from depression by accelerating the rate of metabolism. Certain bundles are still in depression because the degree of excitation was insufficient to call all the fibers into play, which may have been due either to the inequality of the transmission of the stimulus over the muscle system or the greater degree of depression in different fibers.

The two animals of the pilocarpine series verify the observation made upon Rat 27 that excitation upon depression is the normal process of recovery from depression. It is shown in Table IV that Rat 1 which was given the drug for three months showed a frank depression, but Rat 2, which was allowed to recover for two weeks after the same administration of the drug as in the case of Rat 1, showed a recovery from depression. There was no evidence in Rat 2 of its previous depressed state. The hyperchromatic fibers of Rat 2 were almost three times as large as the hyperchromatic fibers of Rat 1, but the nuclei did not increase proportionately, so that the relation of nuclear increase to cytoplasmic increase was two to three. This is evidence that the metabolism of the recovery from depression favors the cytoplasm similarly to the metabolism of excitation.

The dogs, whether normals or experimentally changed animals, demonstrate an identity of reaction to stimulation regardless of the kind of stimulation but, as in the rat, dependent upon the quantitative degree of stimulation. It

should be stated, however, that the dog's heart was much more resistant to experimental changes than the rat's. All of the normal control dogs and the Muscular Exercise series showed some fibers in all stages of excitation with the possible exception of the final stages. They are characterized by the identical changes found in rats. Muscular Exercise 41 and 45, the experimental controls, showed a slight depression with adaptive changes identical in kind and degree with those of a similar degree of depression in the rat.

Muscular Exercise 43, Normal Dog 31, and the Rabies Dog 37, all showed the complex condition of depression superimposed upon excitation in agreement with their physiological state (see experimental data). The physiological depression of Normal 31 was unsuspected until the anatomical diagnosis led to the investigation of his record in the physiological laboratory. The degree of previous excitation was greatest in Muscular Exercise 43 and least in Normal 31; the greatest degree of depression was found in the Rabies animal and least in Normal 31, all of which can be verified by reference to Table IV.

Dog 36 which was given strychnine showed only an early excitation with longitudinal splitting and globular degeneration about the nucleus of some of the fibers.

Non-specificity of stimuli. — The kinds of stimuli used have been several kinds of drugs, namely, digitalis, cocaine, pilocarpine, strychnine, and caffein; operative shock; heat; toxemia from both bacillary and rabies infections; partial oxygen elimination; and excess muscular exercise: yet the reactions have been only of two kinds, namely, excitation or depression, although they have been usually complicated by one being superimposed upon the other. Thus, chemical, mechanical, nervous, trophic, and thermic stimuli have only two possible ways of reacting upon the heart, namely, by excitation or by depression. Upon the basis of cytomorphosis, the conception of a specificity of stimuli affecting the heart must be denied just as Dolley ('16) denied any such specificity for the nerve cell and for the liver cell ('22). Therefore, all abnormalities of

heart muscle must be adaptive changes to excitation, to depression, or to one superimposed upon the other, and all pathological anatomy of the heart arising after maturity must be capable of analysis in terms of excitation and depression.

The pathological significance of the changes. — Many changes which have been described come within the scope of pathological anatomy and, therefore, have especial significance to the pathologist. The pathological anatomy resulting from overexcitation comprises those changes which are associated with normal physiological activity carried to a pathological degree. The changes of depression belong to subnormal physiological activity and likewise become pathological according to their degree. From the viewpoint of stimulation, the changes of excitation, of depression, and of depression superimposed upon excitation are consecutive and phases of an identical quantitative process. The process is physiological, but the end results in its opposite degrees are both pathological.

The final state resulting from both excitation and depression is cell death. Both excitation and depression have one set of changes which are associated with a rapid approach to cell death and another set of changes which are associated with a slow death. This statement means that the degenerations and necroses, and the necrobioses and atrophies of the heart, are referred to stimulation.

Dilatation. — Hypertrophy is the state in which the cell is working at its maximum efficiency. This deduction may be drawn because the range of greatest efficiency must lie within the metabiotic cell and the largest metabiotic cell with the largest amount of organized material must be the most functionally efficient cell. From this association of maximum efficiency and irritability and from the fact that its sarcomeres show the greatest degree of tetanic contraction, demonstrated by having the shortest length, it is demonstrated to be the cell in the greatest degree of tone.

The break in the metabiotic adjustment of the rate and intensity of stimulation to the metabolism conditions a progressive loss of tonicity. This begins on the side of excitation with

the Hodge cell, and on the side of depression with the shrinkage of the fiber and the piling up of chromatic material within the nucleus. This loss of tone is made morphologically evident by the elongation of the sarcomeres and finally in both excitation and depression by a shrinkage in the volume of the sarcomere, although there is still a progressive increase in length. Measurements of the depressed cells and of the cells in the final stage of excitation show a fiber of greater length but smaller cross sectional area. Taking the ventricle as a whole, this conditions a larger cavity with a thinner wall. Such a condition is called dilatation.

Thus dilatation is an end result of both excitation and depression. Examples of dilatations from depression are most commonly those resulting from undernutrition, such as in anemia and leukemia and those from toxic doses of most drugs. The most striking examples of a dilatation from physiological overwork are those of the temporary cardiac dilatation of the Marathon runner and of the mountain climber. Other examples of an excitation dilatation are overwork from valvular deficiencies and from toxic doses of pure cardiac excitant drugs. The most common dilatations which the clinician meets are those resulting from depression superimposed upon excitation such as occur in most toxic diseases of the heart.

For the sake of completeness, the gross condition of the heart from the onset of the loss of tone to the onset of a recognizable excitation dilatation should be mentioned. From the Hodge cell up to, but not including, the end stage of excitation, exhaustion, there is a progressive loss of tone and a progressive increase in the cross sectional area of the fiber. This conditions a thicker walled heart as well as a greater increase in its length and volume. Such a condition is a pseudo-hypertrophy which is a transition stage to dilatation. This transition through an enlarged heart must occur in all excitation dilatations and a striking example of it is the pseudo-hypertrophic cloudy swelling of infectious diseases which end in dilatation.

Vacuolar degeneration. — The end stage of the immediate reaction to overexcitation is not only an elongated fiber but is

also associated with excessive edema, the formation of vacuoles, and the replacement of the cross striations and fibrillae with a foam-like structure which exemplifies the text book picture of vacuolar or hydropic degeneration. It has already been pointed out that this change is found in many normally functioning animals. It passes unnoticed in the normal animal because relatively few fibers are involved. It is only when the degree of excitation is so great that a greater number of fibers is found in this state that the edema is recognized by giving to it a name which implies a pathological significance. The process is physiological because it is found in normal animals but it has been carried by overstimulation to a pathological degree.

Hyaline degeneration. — On the side of depression, the regression from the metabiotic state is associated with a progressive loss of tone, a progressive deficiency of functional energy production and of metabolism. These are made morphologically evident by an increase in the length of the sarcomeres and a progressive shrinkage of the cell and a progressive loss of the differentiated substance, cross striations and fibrillae as the end stage, the hyaline state, is reached. This hyaline, shrunken cell is suggestive of the text book picture of the so-called hyaline or waxy degeneration, the Zenker's degeneration of muscle fibers. The cytoplasm stains a deep almost homogeneous red and shows no evidence of cross striations. It seems that this so-called hyaline degeneration is simply the end stage of acute depression atrophy, although its exact relationship demands further investigation.

Cloudy swelling. — The adaptive changes of depression superimposed upon excitation are of importance because it is probably this combination of factors which is met with more often in disease than either excitation or depression in the pure state. The excitation side of the morphological complex is the swelling of the fiber, the globular degeneration of the cross striations and vacuolization of the sarcoplasm, while the depression side is a condensation of the edematous sarcoplasm into granules and hyperchromatism followed by karyolysis.

The swelling and granular appearance of the sarcoplasm, the hyperchromatism followed by karyolysis, and the degeneration of the cross striations and of the fibrillae are the complex of changes which are typical of the text book descriptions of cloudy swelling. Overexcitation alone furnishes a very similar picture which is probably very often confused with cloudy swelling proper, but the combination of the two phases is necessary to the typical state. The pathological term can at least be more fittingly applied to the complex than to the changes of pure excitation because the factor of depression which enters into the complex is not found in normal animals and suggests a more pathological significance.

Necrobiosis, atrophy. — The three degenerative states which have just been described, namely, vacuolar degeneration, hyaline degeneration and cloudy swelling, are respectively the immediate changes of overexcitation, the immediate changes of depression and the immediate changes of depression upon those of excitation. If the rate and intensity of the stimuli are of a less degree but carried over a greater length of time the regressive processes are slower, the cytological changes are less marked and the process is one of necrobiosis. The late stages of necrobiosis are degrees of atrophy. The end state of cytomorphosis is thus shown to be cell death regardless of whether the adaptation is to overstimulation or understimulation or whether the process is completed in a short time, degeneration and necrosis, or whether the process is extended over a longer time, necrobiosis and atrophy.

In the case of excitation, there is an identity of the processes of immediate cell degeneration and death and of remote cell death, as follows. The first stage of the immediate reaction is a hypertrophy. But, if the rate and intensity of the stimuli are not properly adjusted to the nutritional state of the fiber, this hypertrophic state is soon upset by the failure of the metabolism to keep up with the overexcitation and katabolism exceeds anabolism. This relative predominance of katabolism progressively becomes more prominent until it may reach the state of complete organic exhaustion of the specific structure

of the cell, namely, the fibrillae and the cross striations. At this stage the nuclear materials are also of such a small amount that the life of the cell, which depends upon the presence of nuclear as well as cytoplasmic substances, is endangered and the state of cell death, necrosis, is approximated. Likewise, the secondary or remote reaction to regulated overstimulation leads to the state of hypertrophy. However, all text books agree that this state eventually gives down, the katabiotic processes exceed the anabiotic processes and the cell comes to organic exhaustion, a senile atrophy, through the process of necrobiosis. The cells in the process of remote necrobiosis and those in the process of immediate necrosis differ morphologically only because the swollen cell is full of its waste products which have a high osmotic pressure, while the necrobiotic process is slower and the cells are able to get rid of such waste products.

On the side of depression, the immediate reaction to understimulation is shrinkage of the cell and then of the nucleus. The process is one of progressive anoxidative and metamorphic metabolism with the end result of hyaline or Zenker's degeneration, and fatty change, that is, with a loss of the specialized structure of the cell. Likewise, with a less intense degree of depression acting continuously over a longer period of time, the progressive anoxidative metabolism through its deficient synthesis produces cell atrophy and eventual necrosis. However, the perverted metabolism commonly conditions frank degenerations in association with atrophy, such as fatty degeneration and melanin pigmentation (Dolley, '17).

Intercalated discs. — It has been observed that intercalated discs are found in all animals, but are more prominent and in greater numbers in the complex of depression superimposed upon excitation. Their position is always on Dobie's line, but they do not always follow the same line across the entire fiber. Sometimes they form a stairstep on three or even four different lines. Their significance has been questioned. They are not artifacts, as has been claimed by some, for they serve as anatomical barriers during the life of the fiber. It is demonstrated

that the stimulus to construction is not carried across these discs in two different ways. The first is that on one side is usually found an edematous segment while on the other side is a less active or a depressed segment, that is, the remote segment undergoes depression from disuse. The second is that almost invariably the degree of contraction or relaxation differs on the two sides of the disc. Usually, the less active side is in relaxation and the edematous side is in some degree of contraction.

Segmentation and fragmentation. — J. B. MacCallum ('99, 409) defines segmentation as either a clean or a stairstep break across the breadth of the fiber always occurring at the cement line between muscle segments. MacCallum's "cement lines" are now more commonly known as intercalated discs which have been described above. He defines fragmentation as an irregular break across the breadth of the fiber occurring at some degenerated area.

When breaks occur at some point other than on the intercalated disc and are not explained as fragmentation from degenerations, they are probably artifacts. Some writers have said that all fragmentations and segmentations are artifacts due to a dull knife. It can be said that a dull knife will create artifacts which are similar to antemortem segmentation and fragmentation but which differ from each of them in three respects. Segmentation is differentiated from artifacts in that, first, they do not show the deeply stained intercalated disc adhering to the end of one segment; second, they do not show different stages of contraction on the two sides of the broken fiber, which confirms MacCallum; and third, they do not show different stages of excitation and depression on the two sides of the broken fiber as does true antemortem segmentation. Fragmentation is differentiated from artifacts in that, first, antemortem fragmentation is characterized by a wrinkling and retraction of the broken ends which seem to indicate that the break resulted from a too great stretch of the degenerated fiber with the result that the fiber broke and the ends snapped apart.

The second and third characteristics are the same as those of segmentation.

True fragmentation has been found to be much more rare in rat and dog hearts than in the human heart. No detailed study of the human heart has been made, but a comparison of the human heart with the rat and dog heart was made to find some explanation for this fact. It has been found that degeneration in the rat and dog hearts is principally in the longitudinal direction and in the human it is in the transverse direction. This suggests that the relative frequency of fragmentation in the human heart is due to the tendency to transverse degeneration, as MacCallum claimed. This would also explain the relative infrequency of fragmentation in the rat and dog hearts which have the tendency to longitudinal instead of transverse degeneration.

(In conclusion, I wish to acknowledge that I have consciously used the work of Dr. D. H. Dolley upon the nerve cell as a criterion for this work on the heart muscle. I make this acknowledgment because I realize that credit has probably not always been given where credit is due and because I realize that nothing has been added to the study of the fundamental relation of stimulation to cytomorphosis beyond his work on the nerve cell. I also wish to express my appreciation to Dr. Dolley for his personal direction of the work and for his valuable suggestions and constructive criticism which I have received during the writing of this paper.)

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VITA

William Dean Collier was born at Trenton, Missouri, January 15, 1897. He was one of three children, the only son, born to Weltha and the late James Lewis Collier. He entered public school at the age of seven and graduated from Trenton High School in 1915.

In the fall of 1915, he entered the University of Missouri and pursued the prerequisite requirements for entrance into the School of Medicine. He entered the School of Medicine in 1917, and was graduated from the University in 1919 with the degree of Bachelor of Arts and a certificate of completion of the first two years in the School of Medicine. He entered the Graduate School at the same institution and studied in Pathology under the direction of Dr. D. H. Dolley. He completed the requirements for the degree of Master of Arts in 1920 which was formally conferred in 1921.

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